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(54) Title: NOVEL PHARMACEUTICAL COMPOSITION CONTAINING THE ACE INHIBITOR RAMIPRIL AND A DIHYDROPYRIDINE COMPOUND

(57) Abstract

A pharmaceutical composition which is a combination of the ACE inhibitor ramipril and a calcium antagonist of one of the dihydropyridine type compounds felodipine, nitrendipine, nifedipine and lacidipine. The pharmaceutical composition is for use in the therapy and treatment of hypertension.

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NOVEL PHARMACEUTICAL COMPOSITION CONTAINING THE ACE INHIBITOR RAMIPRIL AND A DIHYDROPYRIDINE COMPOUND

Field of the Invention

The present invention being a new pharmaceutical composition is related to a novel pharmaceutical preparation for oral administration and the use of this pharmaceutical preparation in the therapy of hypertension and of diseases in the cardiovascular system and secondary effects thereof in mammals including man. It is also related to compositions and to methods of preparing said pharmaceutical preparations. The pharmaceutical preparation is a fixed unit dosage form of the long-acting angiotensine converting enzyme (ACE) inhibitor, ramipril, in instant release form and a calcium antagonist of the dihydropyridine type i.e. a calcium channel blocking agent (dihydropyridine compound) in an extended release formulation.

The present invention also relates to solid preparations which are fixed combinations of the long acting ACE inhibitor ramipril in instant release form and a dihydropyridine compound such as the vascular selective drug felodipine in extended release form having the characteristic of achieving an effect over 24 hours after once daily administration. The pharmaceutical preparations of the present invention retain a good therapeutic effect in the treatment of hypertension even when the active drugs are administered in low doses. The pharmaceutical preparations reduce the dose related adverse events which result from administering higher doses of each of the drugs separately. The pharmaceutical preparations of this invention simplify the regimen and improve patient compliance.

Background of the Invention

ACE inhibitors are compounds which inhibit the conversion of angiotensine I into

the active angiotensine II as well as the breakdown of the active vasodilator bradykinin. Both of these mechanisms lead to vasodilation. Such compounds have been described in, for example, EP 158927, EP 317878, US 4,743,450, and US 4,857,520. Ramipril (disclosed in EP 079022) is a long-acting ACE inhibitor. Its active metabolite is the free acid ramiprilat, which is obtained in vivo upon administration of ramipril. In hypertensive patients administration of ramipril is known to cause a reduction in peripheral arterial resistance and thus a reduction of the blood pressure without a compensatory rise in heart rate. It is being used in the treatment of hypertension and congestive heart failure. Furthermore, ramipril has been shown to reduce mortality in patients with clinical signs of congestive heart failure after surviving an acute myocardial infarction. Ramipril has been suggested to have an added advantage over many other ACE inhibitors due to its pronounced inhibition of ACE in tissues resulting in organ protective effects in e.g. the heart, lung, and kidney.

Ramipril substance is sensitive to high temperature, moisture or compression and therefore, upon formulation into pharmaceutical preparations needs special attention in order to retain its stability (US 5,151,433).

Calcium antagonists are compounds which influence the inflow of calcium ions into cells, in particular into the cells of smooth muscles. Such compounds of the dihydropyridine type have been described in, for example, GB 1358951 (nitrendipine), US 3,644,627 (nifedipine), EP 007293 (felodipine), and GB 2164336 (lacidipine).

The most common adverse events which are observed in clinical use of the ACE inhibitor and the calcium antagonists of this invention are headache, coughing, peripheral oedema, flush, dizziness, fatigue and nausea.

Some dihydropyridines, for example nifedipine and felodipine are decomposed

when exposed to light, and therefore, upon handling and formulation into pharmaceutical preparations need special attention in order to retain their stability.

Combinations of ACE inhibitors and calcium antagonists of dihydropyridine type in the treatment of hypertension have been described in, for example EP 488059, EP 180785 and EP 265685.

Bainbridge, A.D. et al. (Br.J. Clin. Pharmac. 1993, 36: 323-330) have studied the use of the angiotensin converting enzyme inhibitor ramipril and an extended release formulation of the dihydropyridine calcium channel antagonist felodipine given in free combination as separate dosage forms.

In US 4,703,038 solid combinations for oral administration of certain ACE inhibitors and certain dihydropyridine compounds including i.a. nitrendipine and felodipine are described. This document also describes a method of treating hypertension in man using such combinations. US 4,703,038 does not, however, disclose ramipril as an ACE inhibitor. Neither does it describe the use of extended release formulations of dihydropyridines.

In US 5,236,933 the use of combinations of certain ACE inhibitors including i.a. ramipril, and certain calcium antagonists, i.a. felodipine have been described in the prevention and/or treatment of proteinuria.

Description of the Invention

The term "instant release" as used herein defines the release of an active drug component that conforms with the criteria in USP XXII under entry "<711> Dissolution" when Q=75%, the time interval is 60 minutes and the dissolution medium is the one specified in the Examples 5-8 below.

The term "extended release" as used herein defines the dissolution of the active drug component from the dosage form over an extended period of time, i.e. for more than 6 hours as measured with the testing method described in Examples 5-8 below.

The term "fixed unit dosage form" as used herein defines a physical embodiment containing more than one active drug component, which embodiment has a heterogenous structure.

Dose figures of pharmaceutically acceptable salts of the active drug given herein relate to the amount of the corresponding free base or acid.

The present invention provides a solid, fixed unit dosage form for oral administration, for example a tablet or a capsule, of an instant release formulation of the long acting ACE inhibitor ramipril or a pharmaceutically acceptable salt of ramipril, and an extended release preparation of a dihydropyridine selected from the group consisting of felodipine, nitrendipine, nifedipine, and lacidipine or a pharmaceutically acceptable salt thereof. Said solid, fixed unit dosage form is effective and tolerable after once daily dosing. Most preferred of the dihydropyridines is felodipine or a pharmaceutically acceptable salt thereof. The choice of an instant release formulation of the long acting ACE inhibitor ramipril and an extended release preparation of a dihydropyridine both contribute to the optimal use of both drugs thereby minimizing the adverse effects while still being effective against elevated blood pressure.

The molecule corresponding to ramipril has five chiral centers and can, thus, occur in 32 different enantiomeric forms. The enantiomer with the name (2S,3aS,6aS))-1-[N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-octahydro-cyclopenta[b]pyrrol-2-carboxylic acid is preferred. This compound is called ramipril.

Pharmaceutically acceptable salts of ramipril are, for example, salts with pharmaceutically acceptable amines or inorganic or organic acids such as, for example, HCl, HBr, H_2SO_4, maleic acid, fumaric acid, tartaric acid and citric acid.

Felodipine has one chiral center and can, thus, occur in two different enantiomeric forms. The vasodilatory effect of the S form is stronger than the vasodilatory effect of the R form. However, both the S form and racemic mixtures of the S form and the R form can be used.

Pharmaceutically acceptable salts of felodipine can be prepared from inorganic and organic acids including for example acetic, benzene-sulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethonic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, and p-toluene-sulfonic acids.

An extended release formulation can, for example, be constructed to give a hydrophilic gel matrix wherein the active substance is enclosed and which upon contact with aqueous solutions will swell to permit release of the active substance by diffusion and/or attrition.

In order to prevent decomposition of ramipril substance by the action of moisture during storage or compression during the manufacturing process the substance is, according to the present invention preferably powder-coated when included in a compressed part of the dosage form. The dihydropyridine substance is light sensitive and is, therefore, protected by a coating layer.

The dose range of ramipril in the combined fixed unit dosage forms is 1-10 mg. The dose range in the combined fixed unit dosage forms is, for felodipine

1-10 mg, for nitrendipine 2-40 mg, for nifedipine 5-70 mg and for lacidipine 1-8 mg.

Most preferred dose range in the combined fixed unit dosage forms is, for ramipril 1-5 mg, for felodipine 1-5 mg, for nitrendipine 5-20 mg, for nifedipine 10-60 mg and for lacidipine 2-6 mg.

A preferred form of the present invention consists of a solid fixed unit dosage form for oral administration which is a low dose combination of an instant release formulation of 1-5 mg of the long acting ACE inhibitor ramipril or a pharmaceutically acceptable salt thereof, and an extended release formulation of 1-5 mg of the vascular selective calcium antagonist felodipine or a pharmaceutically acceptable salt thereof. Especially preferred dose intervals for this preferred form of the invention are 1-3 mg of ramipril and 1-3 mg of felodipine. The preferred dosis quotient between ramipril and felodipine in the preferred form of the present invention is 1:1.

The pharmaceutical preparations of the present invention are for once daily administration utilizing the different blood pressure lowering mechanisms of the ACE inhibitor ramipril in an instant release formulation and a dihydropyridine compound selected from the group consisting of felodipine, nitrendipine, nifedipine, and lacidipine in an extended release formulation. The bioavailability of the ramipril component of the pharmaceutical preparation according to the present invention as measured by the blood plasma concentration of ramiprilat is equivalent to that of the same component administered separately, see Example 1. Also the bioavailability of the dihydropyridine component of the pharmaceutical preparation is equivalent as measured in the same way, see Example 2. The compositions of tablets which were tested are shown in Example 12.

The use of a low dose of the two active components and the extended release of

the dihydropyridine component of the pharmaceutical preparations of the present invention administered once daily give a lowering effect on blood pressure but no compensatory increase in heart rate. It is effective in the treatment of systolic as well as diastolic hypertension. The pharmaceutical preparation is particularly effective in the treatment of systolic hypertension. So administered the preparations have a beneficial influence upon conditions of and associated with high blood pressure (hypertension) in mammals including man. Examples 3 and 4 illustrate the effectiveness of the pharmaceutical preparations of the invention in comparative tests between either ramipril or felodipine and solid fixed combination dosage forms of ramipril and felodipine. It can be seen that there is a surprisingly high degree of reduction in the systolic and diastolic blood pressure of the combined low dose (2.5 mg + 2.5 mg of ramipril and felodipine) preparation in the example in comparison both with each of the components in monotherapy and with the fixed combined preparation of the components in higher (5 mg + 5 mg) dose.The incidence of the most common adverse events during administration of an ACE inhibitor (dizziness, headache, fatigue, nausea and coughing) are low and comparable with that of placebo. The adverse events of administration of dihydropyridine calcium antagonists (increased heart rate, flushing, peripheral oedema, headache and dizziness) are also low and comparable to placebo.

Above all it is evident from Examples 3 and 4 that the most bothersome adverse event of administration of ACE inhibitors, namely coughing, and of administration of dihydropyridine calcium antagonists, namely peripheral oedema and flushing is less common with the low dose combination compared with the monotherapies (F5 and R5).

The release of the respective components in in vitro tests can be seen in Examples 5 to 8.

The pharmaceutical preparation is formulated as a combined solid fixed unit

dosage form for oral administration which in combination with the once daily administration facilitates the regimen and improves patient compliance.

The combined solid fixed unit dosage forms of the present invention can be for example capsules or tablets, which optionally can be coated.

As examples of formulations of ramipril which can be enclosed into capsules can be mentioned ramipril in the form of powder or granules, optionally attached to a carrier substance, and tablets. Examples of extended release preparations of dihydropyridine which can be enclosed into such capsules are granules or tablets. A capsule wherein the ramipril substance is attached to a carrier substance and the dihydropyridine is enclosed in a tablet core consisting of a hydrophilic gel matrix and the process for manufacturing the same is illustrated in Example 9.

Examples of the construction of tablets as fixed unit dosage forms of ramipril and an extended release dihydropyridine portion are shown in Figure 1, 2 and 3.

Figure 1 illustrates a tablet where the dihydropyridine ER (D) matrix preparation is enclosed in a surrounding layer containing instant release ramipril (R) substance. Such a tablet can be manufactured in a suitable tabletting machine. Alternatively, the matrix containing dihydropyridine can be compressed to tablets in a tabletting machine and then coated with a coating containing ramipril. One tablet of this type is illustrated in Example 10.

Figure 2 illustrates a tablet where the ramipril (R) component is placed at the upper part of the matrix containing the dihydropyridine ER (D) preparation. The instant release ramipril component is contained in a smaller part which is enclosed in a larger, separate part containing the felodipine extended release preparation. Instant release of ramipril is achieved since it is not entirely enclosed in the matrix. Such a tablet can be manufactured in a suitable tabletting machine.

Figure 3 illustrates a tablet which is composed of one tablet layer containing the instant release ramipril (R) substance joined to another tablet layer containing the dihydropyridine ER (D) preparation resulting in a multiple layer tablet. The two tablet layers can be joined directly to each other or via one or more intermediate layers (L).

Example 1

Pharmacokinetics of ramiprilat on treatment day 7 following once daily administration of the present invention according to Example 12 and a free monotherapy ramipril tablet (B). both given at 5 mg dosages, in 18 healthy volunteers. C_{max} is the peak plasma concentration, t_{max} is the time after administration the peak concentration was attained. C_{min} is the lowest plasma concentration during the period. AUC is the area under the plasma concentration curve. SD is the standard deviation. p-values greater than 0.05 mean that no statistical significance in the quotient or the difference is at hand.

Parameter		Treatment		Comparison
		A	B	
C_{max} (nmol/l)	mean	23.8	24.2	A/B
	SD	13.8	12.2	p=0.57
t_{max} (h)	mean	2.8	2.5	A-B
	SD	1.1	0.9	p=0.35
C_{min}(nmol/l	mean	3.9	4.1	A-B
	SD	1.2	0.9	p=0.64
AUC (nmol·h/l)	mean	211.1	213.3	A/B
	SD	54.7	45.3	p=0.94

Example 2

Pharmacokinetics of felodipine on treatment day 7 following once daily administration of the present invention according to Example 12 and a free monotherapy felodipin tablet (B), both given at 5 mg dosages, in 18 healthy volunteers. C_{max} is the peak plasma concentration, t_{max} is the time after administration the peak concentration was attained. C_{min} is the lowest plasma concentration during the period. AUC is the area under the plasma concentration curve. SD is the standard deviation. p-values greater than 0.05 mean that no statistical significance in the quotient or the difference is at hand.

Parameter		Treatment		Comparison
		A	B	
C_{max} (nmol/l)	mean	2.8	3.2	A/B
	SD	1.0	1.3	p=0.18
t_{max} (h)	mean	4.6	4.6	A-B
	SD	1.9	2.6	p=0.91
C_{min}(nmol/l	mean	0.9	0.9	A-B
	SD	0.3	0.3	p=0.16
AUC (nmol·h/l)	mean	38.4	39.5	A/B
	SD	14.5	12.9	p=0.33

Example 3

The antihypertensive efficacy and tolerability of the combined fixed unit dosage form of felodipine ER and ramipril in doses of 5+5 mg and 2.5+2.5 mg were compared with those of individual monotherapies of felodipine ER 5 mg and ramipril 5 mg and with placebo in this double-blind, five armed parallel group multicentre study. Patients with primary hypertension whose supine diastolic blood pressure (DBP) was 95-110 mmHg inclusive at two separate occasions during the 4-6 week placebo run-in period were randomised to treatment either with

felodipine ER-ramipril 5+5 mg (FR 5+5), felodipine ER-ramipril 2.5+2.5 mg (FR 2.5+2.5), felodipine ER 5 mg (F5), ramipril 5 mg (R5), or placebo.

Eleven-hundred and three (1103) patients were enrolled and nine-hundred and thirty-nine (939) patients from six countries (Australia, Canada, Denmark, Italy, New Zealand and Sweden) were randomised into this study. Eight-hundred and seventy (870) patients completed the study. In the analyses 518 males and 421 females with a mean age of 57 years, ranging from 24 to 86 years, were included.

Supine diastolic blood pressure (DBP) and supine systolic blood pressure (SBP) were measured 4 hours and 24 hours post dose at randomisation (baseline) and after 11 and 12 weeks of treatment.

Mean reduction in supine DBP and SBP from baseline to average of 11 and 12 weeks treatment (p-values less than 0.05 are statistically significant.)

Supine DBP (mm Hg)

Administered agent	4 hours	24 hours
Placebo	-6.5	-5.9
FR 2.5+2.5	-12.4	-10.1
FR 5+5	-14.0	-11.5
F5	-11.4	-9.4
R5	-8.9	-7.6

Supine SBP (mm Hg)

Administered agent	4 hours	24 hours
Placebo	-6.8	-5.6
FR 2.5+2.5	-17.9	-14.2
FR 5+5	-20.1	-14.8
F5	-13.3	-11.9
R5	-12.1	-8.6

All active treatments gave a statistically significant reduction in supine DBP (24 hours and 4 hours post dose) from baseline to the average of 11 to 12 weeks of treatment compared with placebo.

Mean differences in change (from baseline to average 11 to 12 weeks) in blood pressure. Comparison between combination treatments and placebo.

Comparison	Supine DBP				Supine SBP			
	24-hr	p-value	4-hr	p-value	24-hr	p-value	4-hr	p-value
FR 2,5+2,5 vs placebo	-4.5	<0.001	-6.6	<0.001	-9.0	<0.001	-13.2	<0.001
FR 5+5 vs placebo	-6.0	<0.001	-8.0	<0.001	-9.6	<0.001	-15.0	<0.001

Both treatments with combined fixed unit dosage forms given once daily to hypertensive patients gave a statistically significant reduction in both supine systolic and diastolic blood pressure compared to placebo, both at peak (4 hours post dose intake) and at trough (24 hours post dose intake).

Mean differences in change (from baseline to average 11 to 12 weeks) in supine blood pressure. Comparison between treatments

Comparison	Supine DBP				Supine SBP			
	24-hr	p-value	4-hr	p-value	24-hr	p-value	4-hr	p-value
FR 5+5 vs F5	-1.9	0.015	-2.8	0.004	-1.9	0.198	-7.3	<0.001
FR 5+5 vs R5	-3.9	<0.001	-5.7	<0.001	-6.9	<0.001	-8.5	<0.001
FR 2.5+2.5 vs F5	-0.4	0.617	-1.3	0.166	-1.3	0.379	-5.5	0.001
FR 2.5+2.5 vs R5	-2.4	0.003	-4.2	<0.001	-6.3	<0.001	-6.7	<0.001

The treatments with combined fixed unit dosage forms also gave a significantly greater reduction in both supine systolic and diastolic blood pressure than the individual monotherapies.

Furthermore, the low dose combination is equally (compared to felodipine) or more (compared to ramipril) effective in reducing supine diastolic and systolic blood pressure than double the dose of the individual monotherapies.

Similar results were obtained in the standing position indicating no orthostatic effects with any of the treatments.

Most common adverse events (% of patients)

	N=187 Plac	N=186 FR2.5+2.5	N=190 FR5+5	N=188 F5	N=188 R5
Headache	9.1	5.9	7.4	6.9	5.9
Dizziness	5.3	4.3	3.2	5.3	6.4
Fatigue	1.6	1.1	2.6	<1.0	3.2
Nausea	2.7	1.6	1.1	1.6	3.2
Oedema peripheral	3.7	3.8	4.7	5.9	1.6
Feeling warmth/Flush	<1.0	3.8	2.6	7.4	2.7
Coughing	2.7	5.9	7.4	4.8	10.6

Both therapies with combined fixed unit dosage forms were very well tolerated. The number of patients with adverse events and number of patients with adverse events causing stop of therapy in the fixed combination groups were comparable to that of placebo.

The incidence of the most common adverse event observed during administration of an ACE inhibitor (dizziness, headache, fatigue, nausea and coughing) and during administration of dihydropyridine calcium antagonists (increased heart rate, flushing, peripheral oedema, headache and dizziness) tended to be lower during therapy with combined fixed unit dosage forms than during therapy with the individual monotherapies. Above all, this is evident for the most bothersome adverse events with ACE inhibitors coughing, and dihydropyridine calcium antagonists, peripheral oedema and flush.

Example 4

Result of a clinical study evaluating efficacy and tolerability of a combined fixed unit dosage form of felodipine ER and ramipril in the dose 2.5 + 2.5 mg (FR

2.5+2.5) in comparison with the individual monotherapies ramipril 2.5 mg (R 2.5) and felodipine ER 2.5 mg (F 2.5) given once daily. The study was double-blind, multicentre, 3-armed parallel group design. Similar inclusion criteria as the study of Example 1 and treatment length 12 weeks. About 600 patients completed the study. Results of measurement of blood pressures 24 hours post administration.

Mean reduction in supine DBP and SBP from baseline to 12 weeks (Pressures in mm Hg). Supine BP measured at 24 hours.

Administered agent	Supine DBP		Supine SBP	
FR 2.5+2.5		-12.0		-15.5
F 2.5	-9.6		-12.0	
R 2.5	-9.8		-11.3	

Adjusted mean difference in change from baseline to 12 weeks. Supine BP measured at 24 hours.

Comparison	Supine DBP		Supine SBP	
	24 hr	**p-value**	**24 hr**	**p-value**
FR 2.5+2.5 vs F2.5	-2.4	0.01	-4.0	0.02
FR 2.5+2.5 vs R2.5	-1.6	0.07	-3.9	0.02

Most common ADEs (% of patients)

	N = 216 FR 2.5 + 2.5	N = 213 F 2.5	N = 213 R 2.5
Headache	5.1	5.6	4.2
Back pain	3.7	3.8	6.6
Coughing	6.0	1.4	5.2
Vasodilatation	3.7	3.3	1.9
Infection	1.9	3.3	2.3
Peripheral oedema	2.3	3.8	0.9
Dizziness	2.3	1.9	2.3

Example 5

Capsule containing ramipril 2.5 mg on a carrier and a felodipine 5.0 mg compressed unit. Ramipril is released quickly ("instant release") and felodipine is released during an extended period ("extended release").

Dissolution of ramipril/felodipine in vitro was tested in 500 ml of a 0.1 M phosphate buffer pH 6.5 with addition of 0.4 % of cetyl trimethyl ammonium bromide (CTAB). USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets, operated at 100 rpm was used. Release figures, in per cent, denote average values and within brackets minimum - maximum values. 6 capsules were tested. For the composition of the capsule, see Example 9.

Time (h)	Ramipril	Felodipine
0.5	102 (100-103)	not determined
1	not determined	11 (11-13)
4	"	61 (58-64)
7	"	101 (99-104)

Example 6

Dissolution of ramipril/felodipine in vitro from a coated tablet containing 2.5 mg/5 mg respectively of the active substances tested in 500 ml of a 0.1 M phosphate buffer pH 6.5 with addition of 0.4% of cetyl trimethyl ammonium bromide (CTAB). USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets, operated at 100 rpm, was used. Release figures in per cent, denote average value and within brackets minimum - maximum values. 6 tablets were tested. For the composition of the tablet, see Example 10.

Time (h)	Ramipril	Felodipine
0.5	103 (99-107)	not determined
1	not determined	9 (8-9)
4	"	53 (50-56)
7	"	90 (86-94)

Example 7

Dissolution of ramipril/felodipine in vitro from a layered tablet containing 2.5 mg/2.5 mg respectively of the active substances in 500 ml of a 0.1 M phosphate buffer pH 6.5 with addition of 0.4% of cetyl trimethyl ammonium bromide (CTAB). USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets, operated at 100 rpm, was used. Release figures, in per cent, denote average value and figures within brackets denote minimum-maximum values. 6 tablets were tested. For the composition of the tested tablet, see Example 11.

Time (h)	Ramipril	Felodipine
0.5	97 (90-103)	not determined
1	not determined	8 (6-9)
4	"	54 (51-56)
7	"	92 (89-94)

Example 8

Dissolution of ramipril/felodipine in vitro from a layered tablet containing 5 mg/5 mg respectively of the active substances tested in 500 ml of a 0.1 M phosphate buffer pH 6.5 with addition of 0.4% of cetyl trimethyl ammonium bromide (CTAB). USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets, operated at 100 rpm, was used. Release figures in per cent, denote average values and figures within brackets denote minimum-maximum values. 6 tablets were tested. For the composition of the tested tablet, see Example 12.

Time (h)	Ramipril	Felodipine
0.5	94 (89-100)	not determined
1	not determined	12 (12-13)
4	"	60 (58-61)
7	"	95 (93-96)

Example 9

Capsule containing ramipril 2.5 mg on a carrier and a felodipine 5.0 mg compressed unit. Ramipril is released quickly ("instant release") and felodipine is released during an extended period ("extended release").

The felodipine tablet core was constructed according to the hydrophilic gel matrix

principle described in "Hydrophilic Matrix Sustained Release Systems Based on Polysaccharide Carriers" by Colin D. Melia, in Critical Reviews in Therapeutic Drug Carrier Systems, 8(4): 395-421 (1991) in the following way: Two different granulating solutions (I and II) were prepared and the solutions were used for granulating the powder mass (III).

Solution I	mg/tablet
Felodipine	5.00
Polyoxyl 40 hydrogenated castor oil	12.50
Propyl gallate	0.060
Ethanol	30.00
Solution II	
Polyvinyl pyrrolidone	24.00
Ethanol	300.0
Powders in granulate III	
Hydroxypropyl methylcellulose	200.00
Sodium Aluminium silicate	94.00
Lactose	56.00
Microcrystalline cellulose	6.00
Hydroxypropyl methylcellulose	30.00
Sodium stearylfumarate	8.60

The powder mixture was moistened with Solution I while mixing to homogeneity. Then Solution II was added and mixing was continued until homogeneity. Drying of the granulate was performed in a drying oven.

The dry granulate was milled using a Frewitt oscillating granulator. After milling the granulate was mixed with additionally 30 mg per tablet of hydroxypropyl

methyl cellulose (HPMC) until homogeneity and then lubricated with sodium stearyl fumarate. The final mixing was continued for 3 minutes. Compression was performed in a Korsch Pharmapress 100 with 7 x 13 punches (scored). Obtained tablet hardness measured over the longest axis was greater than 20 kP.

The ramipril carrier was manufactured in the following way:

Coating solution	
Ramipril	3.33 g
HPMC	10.00 g
Acetic acid 0.01 M	200 g
EtOH	200 g
Core	
Non-Pareille inert core	210 g
(According to USP monograph for "Sugar Spheres")	

Equipment

Fluid bed (Wurster equipped),

Spray Nozzle: Schlick

Insert tube diameter 50 mm, length 60 mm

The coating process resulted in beads having a ramipril content of 13.5 mg/g. One of the tablets from the above was filled in a hard gelatine capsules, size 00, together with 185 mg of the ramipril containing beads.

Properties of the obtained capsules	
Capsule weight	747 mg
Felodipine content	5.0
Ramipril content	2.4 mg/capsule

Example 10

Tablet containing ramipril in the coat and felodipine in the tablet core. Ramipril is released instantly whereas felodipine is released during an extended period.

The felodipine tablet core was constructed according to the hydrophilic gel matrix principle (See reference example 7) in the following way: Two different granulating solutions (I and II) were made, and these were used to granulate the powder mass (III).

Solution I	mg/tablet
Felodipine	5.00
Polyoxyl 40 hydrogenated castor oil	5.00
Propyl gallate	0.060
Ethanol	30.00
Solution II	
Hydroxypropyl cellulose	10.00
Ethanol	160.00
Powders III	
Hydroxypropyl methylcellulose	100.00
Sodium Aluminium silicate	47.00
Lactose	28.00
Microcrystalline cellulose	3.00
Sodium stearylfumarate	4.20

The powder mixture was moistured with Solution I while mixing to homogeneity. The Solution II was added and mixing continued to homogeneity. Drying of the granulate was performed in a drying oven.

The dry granulate was milled using a Frewitt oscillating granulator. After milling, the granulate was lubricated with sodium stearyl fumarate and the final mixing was continued for 3 minutes. Tabletting was performed on a tabletting machine using 9 mm circular concave punches. Obtained tablet hardness was approximately 7-8 kP measured with a Schleuniger hardness tester.

The felodipine tablets obtained according to the above were used as cores in a coating process applying a coating layer comprising ramipril and, as a binder, hydroxypropyl methyl cellulose (HPMC) 6 cps, dissolved in a mixture of alcohol and an acetic acid water solution.

The tablet cores were coated in the following way:

Coating solution	
Acetic acid sol. 0.01 M	200 g
Ethanol	200 g
HPMC 6 cps	10 g
Ramipril	3.46 g
Cores	
Felodipine ER tablets 5mg, diameter 9 mm (1000 tablets)	206 g

Equipment

Fluid bed (Wurster equipped)

Spray nozzle: Schlick

Insert tube diameter 50 mm, length 60 mm

The HPMC was dissolved in a mixture of the acetic acid water solution and the ethanol, then the ramipril powder was dissolved in this solution. The solution was sprayed onto the tablets using the equipment and under the conditions specified above. Coating may, alternatively, be performed in other conventional equipment, e.g. Accela Coata or coating pans.

Properties of the obtained tablets

Tablet weight	216 mg/tablet
Felodipine content	4.9 mg/tablet
Ramipril content	2.4 mg/tablet

Example 11

Combined instant release ramipril and extended release felodipine layered tablets 2.5 mg/2.5 mg. Composition.

Component	mg/tablet
Ramipril layer	
Ramipril	2.5
Hydroxypropyl methylcellulose	0.4
Lactose	24.0
Maize starch 1500	48.8
Microcrystalline cellulose	24.0
Sodium stearyl fumarate	≤ 1.0
Water purified	q.s.
Felodipine layer	
Felodipine	2.5
Hydroxypropylcellulose	10.0
Hydroxypropyl methylcellulose	100
Lactose	28.0
Microcrystalline cellulose	3.0
Polyoxyl 40 hydrogenated castor oil	2.5
Propyl gallate	0.06
Sodium aluminium silicate	47.0
Sodium stearyl fumarate	≤ 6
Ethanol	q.s.

Coating layer	
Colour iron oxide	about 0.3
Hydroxypropyl methylcellulose	7.4
Paraffin	about 0.1
Polyethylene glycol	1.9
Titanium dioxide	0.8
Water purified	about 64

Ramipril was granulated with hydroxypropyl methylcellulose in purified water. The dried material was classified and mixed with lactose, maize starch and microcrystalline cellulose. Final mixing was made with sieved sodium stearyl fumarate. The felodipine granulate was manufactured separately according to the procedure described in Example 8. The two granulates were then fed into a layer press equipped with two filling stations and compressed into tablets.

The tablets were finally coated with an outer coating layer using conventional equipment.

Example 12

Combined instant release ramipril and extended release felodipine layered tablets 5 mg/5 mg. Composition.

Component	mg/tablet
Ramipril layer	
Ramipril	5.0
Hydroxypropyl methylcellulose	0.9
Lactose	23.5
Maize starch 1500	46.8
Microcrystalline cellulose	23.5
Sodium stearyl fumarate	≤1.0
Water purified	q.s.
Felodipine layer	
Felodipine	5.0
Hydroxypropylcellulose	10.0
Hydroxypropyl methylcellulose	100.0
Lactose	28.0
Microcrystalline cellulose	3.0
Polyoxyl 40 hydrogenated castor oil	5.0
Propyl gallate	0.06
Sodium aluminium silicate	47.0
Sodium stearyl fumarate	≤6
Ethanol	q.s.
Coating layer	
Colours, iron oxides	about 0.3
Hydroxypropyl methylcellulose	7.5
Paraffin	about 0.1
Polyethylene glycol	1.9
Titanium dioxide	0.8
Water purified	about 65

For the manufacturing process see example 11.

Claims

1. A pharmaceutical preparation for oral administration comprising a combination of

a) the ACE inhibitor ramipril, or a pharmaceutically acceptable salt thereof and,

b) a dihydropyridine compound selected from the group consisting of felodipine, nitrendipine, nifedipine, and lacidipine, or a pharmaceutically acceptable salt thereof

characterized by

1) ramipril being in instant release form
2) the dihydropyridine compound being in extended release (ER) form
3) the combination being in a solid fixed unit dosage form.

2. A pharmaceutical preparation according to claim 1 wherein the dihydropyridine compound is felodipine.

3. A pharmaceutical preparation according to claim 1 wherein the dihydropyridine compound is nitrendipine.

4. A pharmaceutical preparation according to claim 1 wherein the dihydropyridine compound is nifedipine.

5. A pharmaceutical preparation according to claim 1 wherein the dihydropyridine compound is lacidipine.

6. A pharmaceutical preparation according to any of claims 1 to 5 wherein the

amount of ramipril or a pharmaceutically acceptable salt thereof is 1 to 10 mg and the amount of the dihydropyridine compound or a pharmaceutically acceptable salt thereof is 1 to 70 mg per dosage unit.

7. A pharmaceutical preparation according to any of claims 1 to 6 wherein the amount of ramipril or a pharmaceutically acceptable salt thereof is 1 to 5 mg and the amount of the dihydropyridine compound or a pharmaceutically acceptable salt thereof is 1 to 60 mg per dosage unit.

8. A pharmaceutical preparation according to claim 6 wherein the amount of each of ramipril or a pharmaceutically acceptable salt thereof and felodipine or a pharmaceutically acceptable salt thereof is 1-5 mg per dosage unit.

9. A pharmaceutical preparation according to claim 6 wherein the amount of each of ramipril or a pharmaceutically acceptable salt thereof and felodipine or a pharmaceutically acceptable salt thereof is 1-3 mg per dosage unit.

10. A pharmaceutical preparation according to claim 8 to 9 wherein the dosis quotient of the components is 1:1.

11. A pharmaceutical preparation according to any of claims 1 to 10 wherein the ER formulation is comprised in a hydrophilic gel matrix.

12. A pharmaceutical preparation according to any of claims 1 to 11 wherein the solid fixed unit dosage form is a capsule.

13. A pharmaceutical preparation according to any of claims 1 to 11 wherein the solid fixed unit dosage form is a tablet.

14. A pharmaceutical preparation according to any of claims 1 to 13 wherein the

ramipril component is included in a coating layer which is surrounding the dihydropyridine ER component.

15. A pharmaceutical preparation according to any of claims 13 or 14 wherein the dihydropyridine ER component is in a tablet layer which is joined to another tablet layer containing the ramipril component, or, optionally, wherein the dihydropyridine ER component is in a tablet layer which is joined, indirectly via one or more layers without active components, to another tablet layer containing the ramipril component.

16. A pharmaceutical preparation according to any of claims 1 to 11, 13 or 14 wherein one of the components is contained in a smaller part which is contained in a larger, separate part containing the other component.

17. A process for the manufacture of a pharmaceutical preparation according to any of claims 1 to 11 or 13 to 16 characterized in that the ramipril and the dihydropyridine ER components are compressed to a tablet in a tabletting machine.

18. A process for the manufacture of a pharmaceutical preparation according to any of claims 1 to 11, 13, 15 or 16 characterized in that a tablet layer containing the ramipril component is joined to a tablet layer containing the dihydropyridine ER substance to produce a combined tablet.

19. A process according to any of claims 17 or 18 characterized in that the tablet product is coated with a pharmaceutically acceptable coating.

20. A process for the manufacture of a pharmaceutical preparation according to claim 12 characterized in that ramipril and an extended release form of dihydropyridine are enclosed into a capsule.

21. A pharmaceutical preparation according to any of claims 1 to 16 for use in the prevention or treatment of diseases in the cardiovascular system, in particular hypertension.

22. The use of a preparation according to any of claims 1 to 16 in the manufacture of a medicament intended for the treatment of diseases in the cardiovascular system.

23. A pharmaceutical preparation according to any of claims 1 to 16 for use in therapy.

24. A pharmaceutical preparation according to any of claims 1 to 16 for use in the prevention or treatment of deseases in the cardiovascular system, in particular hypertension in mammals including man.

25. A method of preventing or treating hypertension in mammals including man comprising the administration of an effective amount of a pharmaceutical preparation according to any of claims 1 to 16 to a patient in need of such treatment.

26. A method of preventing or treating hypertension in mammals including man comprising the administration once per day of an effective amount of a pharmaceutical preparation according to any of claims 1 to 16 to a patient in need of such treatment.

27. A method according to any of claims 25 or 26 wherein the pharmaceutical preparation is administered once daily.

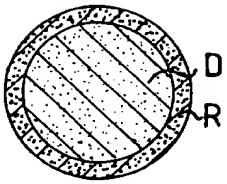

FIG.1A

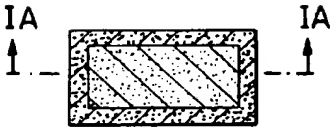

FIG.1B

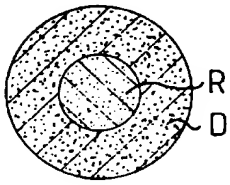

FIG.2A

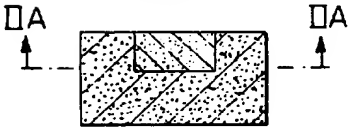

FIG.2B

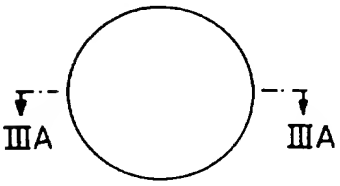

FIG.3A

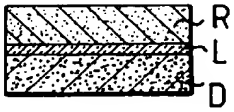

FIG. 3B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00972

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/22, A61K 38/05, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, MEDLINE, EMBASE, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Br J clin Pharmac, Volume 36, 1993, A.D. Bainbridge et al, "The antihypertensive efficacy and tolerability of a low dose combination of ramipril and felodipine ER in mild to moderate essential hypertension" page 323 - page 330	1-10
A	--	11-24
X	Dialog Information Services, File 351, World Patent Index 81-95, Dialog accession no. C93-026534, WPI accession no. 93-059347/08, Polli G P: "Combined time-release calcium channel blocker and ACE inhibitor - used for treating hypertension, congestive heart failure and other coronary diseases", & CA, A, 2070085, 921201, 9308 (Basic)	1-24
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 1995	19.12.95
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00972

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5178867 A (GEORGE V. GUITTARD ET AL), 12 January 1993 (12.01.93), page 6, line 36 - line 68, claims --	1-24
A	EP 0265685 A2 (HOECHST AKTIENGESELLSCHAFT), 4 May 1988 (04.05.88) --	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00972

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25-27
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/10/95

International application No.
PCT/SE 95/00972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5178867	12/01/93	AU-A- 2544992	16/03/93
		CA-A- 2112679	04/03/93
		EP-A,B- 0600033	08/06/94
		FI-A,D- 940787	18/02/94
		JP-T- 6509809	02/11/94
		NO-A,D- 940376	07/02/94
		NZ-A- 244009	24/02/95
		PT-A- 100789	31/05/94
		WO-A- 9303711	04/03/93
		ZA-A- 9206241	04/10/93
EP-A2- 0265685	04/05/88	SE-T3- 0265685	
		AU-B,B- 611863	27/06/91
		AU-A- 7928087	14/04/88
		CA-A- 1317545	11/05/93
		DE-A- 3633496	14/04/88
		DE-A- 3780753	03/09/92
		ES-T- 2043626	01/01/94
		IE-B- 59975	04/05/94
		JP-A- 63096136	27/04/88
		NO-B,C- 175621	01/08/94
		US-A- 5098910	24/03/92